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Fanconi's Anemia and Malignancies

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Patients with Fanconi's anemia (FA) are at a high risk for development of malignancies. It is well-known that leukemia occurs in ~10% of cases, with increasing risk with age. Less commonly recognized is the risk for myelodysplastic syndromes (~5%); the relationship between myelodysplasia and evolution to leukemia remains speculative. What also needs to be emphasized is that older patients have an ever-increasing risk for development of solid tumors, with at least 5% reported to have liver tumors (male:female ratio, 2:1) and an equal number of other cancers (female:male ratio, 3:1, even after exclusion of gynecologic malignancies). Hematologists have tended to focus on aplastic anemia and leukemia. As FA patients live longer, more of the other malignancies will occur, perhaps related to cord blood or bone marrow transplant, or treatment with cytokines. This review identifies the types of tumors for which patients with Fanconi's anemia are at risk.

Key words: Fanconi's anemia, aplastic anemia, cytogenetics, leukemia, myelodysplastic syndrome, cancer

INTRODUCTION

Fanconi's anemia (FA) is an autosomal-recessive disorder, in which homozygotes have a high incidence of birth defects and aplastic anemia [1], as well as increased chromosomal breakage following culture of cells (usually lymphocytes) with clastogenic agents [2]. FA is the most common type of inherited bone-marrow failure syndrome, in which the average age of onset of aplastic anemia is 8 years. It is recognized that these patients are at risk of leukemia [3,4]. Less commonly noted is the fact that other malignancies, such as liver cancers and solid tumors, may also occur. Since patients with FA have a life expectancy that has improved from age 10 years in the cases reported before 1960 to age 30 years in those reported in the last 5 years, some attention needs to be given to the malignant conditions for which these patients are at ever-increasing risk as they move into adulthood. Those who have had bone marrow transplants or gene therapy may be particularly at risk.

The specific pathophysiology of FA is not yet defined, although it is in the category of chromosome-breakage syndromes, and the presumptive defect is in the area of repair of DNA crosslink damage [5]. There are at least five distinct complementation groups [6,7]. The gene for FA complementation group C (FAC) has been cloned and mapped to 9q22.3, but its gene product is a new protein whose function is not yet elucidated [8]. Data are insufficient to determine the relationship between genetic mutations and severity of disease or risk for malignancy, except to suggest that the FAC IVS4 +4 A→T mutation found in Ashkenazi Jewish patients is associated with a severe phenotype with multiple birth defects [9].

There has not been a recent in-depth analysis of the types of malignancies or premalignancies which occur in FA patients. The patterns are unique to FA, and distinct from those which occur in other genetic diseases with cancer potential, such as Bloom's syndrome [10], xeroderma pigmentosum [11], Werner's syndrome [12], ataxia telangiectasia [13], and Li-Fraumeni's syndrome [14]. In FA, the major categories are myeloid leukemias, myelodysplastic syndromes, and tumors involving the liver, oropharynx, gastrointestinal tract, and gynecologic systems. Unfortunately, treatment remains difficult, because of too narrow a therapeutic index for chemotherapy or radiation, due to the underlying DNA instability.

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TABLE I. Leukemia in FA*

Type	Number	Male	Female	Unknown
Acute nonlymphoblastic	73	42	30	1
Myeloblastic	30	18	12	
Myelomonocytic	20	11	8	1
Monocytic	9	5	4	
Erythroleukemia	7	5	2	
Megakaryoblastic	1	1		
Not specified	6	2	4	
Acute lymphoblastic	3	1	2	
Chronic myelomonocytic	2		2	
Acute unspecified	6	3	2	1
Total	84	46	36	2

*Five patients had liver tumors; 1 patient had an astrocytoma.

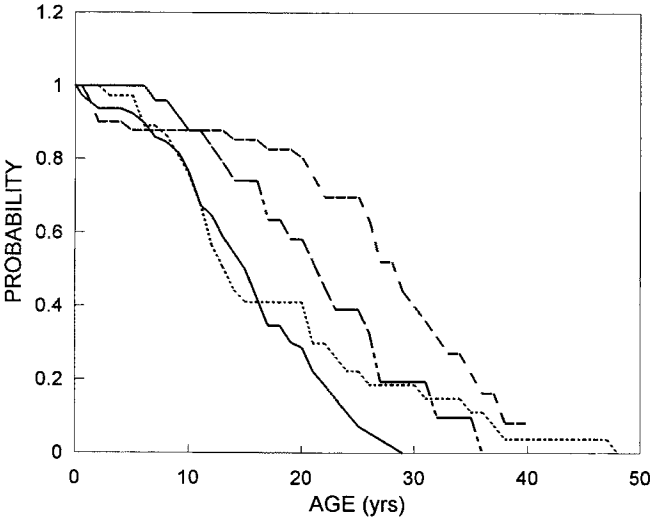

Fig. 1 Kaplan-Meier plot of cumulative survival in Fanconi's anemia following complications. Time is shown as age in years. – – –, cancer, 15/41 withdrawn alive; ——, leukemia, 15/80 withdrawn alive; ——– – –, MDS, 8/25 withdrawn alive; · · · ·, liver disease, 5/37 withdrawn alive. Age or survival data were not available for all patients in the literature.

METHODS

This review provides an analysis of the world's literature from 1927–1994 (see Alter and Young [15] and Young and Alter [16] for many of the references). Ascertainment was through Medline search for "Fanconi" or "Fanconi's Anemia," as well as from the references of papers that were cited in other papers. Cases were included unless it was clear in retrospect that the patient had another condition, e.g., dyskeratosis congenita. Chromosome breakage tests were not always available, since earlier cases antedated such testing. Cases were excluded if results were negative with appropriate testing. In fact, between 60–80% of accepted cases (depending on type of complication, see below) did have documented increased chromosome breakage. The leukemia and cancer diagnoses were accepted as provided by the authors, since examination of original tissues was not possible in this review. Thus, the analyses are of the perceptions provided by the literature cases, which were themselves usually peer-reviewed. Where available, comparison will be made with data published by the International Fanconi Anemia Registry (IFAR). The two sources cannot be combined, because their ascertainment methods differ, and because some of the IFAR cases have in fact been published as case reports and are included in the literature review. All of the data may be underestimates, since complications may have occurred subsequent to completion of the literature reports or of the IFAR reports. However, the converse is also possible, that cases without complications were never reported, and thus the denominator is too low, and the data are overestimates. The important aspect to be noted is not the specific incidences so much as the reality that patients with FA are at progressively increasing risk of cancer as they age; this review summarizes the types of cancers which have been reported.

The number of cases in the review in which sufficient data are provided for analyses is close to 1,000, while most recent IFAR reports included almost 400 patients [17,18]. The proportion of patients who eventually developed aplastic anemia is >80%. The patients are essentially comparable in the types of physical anomalies described [16,17], and in the observation that 20–40% did not have significant birth defects. The number of FA patients in the literature who had one or more malignancy is 148 (15%).

LEUKEMIA

Among the >950 cases analyzed from the literature, there were 84 reports of cases with leukemia (9%), at a mean age of 14 years, with a range of 1 month–29 years. Sixty-eight percent of those with leukemia did have increased chromosome breakage. Twenty of these patients presented with leukemia as their first hematologic problem. These plus an additional 20 patients (for a total of 48%) never received androgen treatment, and thus androgens cannot be construed as etiologic for leukemia. The types of leukemia (Table I) include predominantly those in the myeloid series. There were 30 acute myeloblastic leukemias [19–39] (also, F.H. Gardner, personal communication), 20 acute myelomonocytic leukemias [40–57] (also, S. Lux, personal communication), 9 acute monocytic leukemias [38,45,58–63], 7 erythroleukemias [21,29,33,60,64–69], 6 acute unspecified leukemias [29,42,56,58,70], 5 acute nonlymphocytic leukemias [63,71–73], 2 chronic myelomonocytic leukemias [74,75], and 1 acute megakaryoblastic leukemia [76]. Only 3 cases were reported to be acute lymphoblastic

TABLE II. Preleukemia in FA

	N	%	Interval (years)
Total	32		
Clonal cytogenetic abnormality	31	97	
Marrow			
MDS	13	41	
RA	3	9	
RAEB	5	16	
Normal	3	9	
Aplastic	5	16	
Cellular	2	6	
Not described	1	3	
Leukemic evolution	7	22	0.3–1.3
Decreased, no leukemia	17	53	0–12
Alive, no leukemia	8	25	1–3
Sweet's syndrome	3	9	

leukemia [77–79]. Several patients were described in more than one publication, and thus the number of literature reports exceeds the actual number of cases. Five patients with leukemia had coincidental hepatic tumors discovered postmortem [25,32,47,73,44], one had an astrocytoma [37], and one a retinoblastoma [39].

The leukemias were generally those which are more difficult to treat, and the patients had problems with chemotherapy because of the defect in DNA repair as well as their lack of marrow reserve. The only long-term remissions were for 2, 8, and more than 10 years [54,69,80] (also, K.J. Roozendaal, personal communication). Bone-marrow transplant from human leukocyte antigen-(HLA)-matched sibling donors was successful in only 5 of 13 patients who had leukemia or myelodysplastic syndromes (see Myelodysplastic Syndrome, below) [36,40,81–85], and failed in one patient using an unrelated donor [82]. The projected median survival for untransplanted FA patients with leukemia was age 15 years (Fig. 1), and the interval from diagnosis to death was usually very short. Eighty per cent had died by the time of the reports, at a mean of age 15 years (range, 4 months–29 years).

In the IFAR report [18], leukemia and myelodysplastic syndrome (MDS) were not always distinguished (see Myelodysplastic Syndrome, below). Nevertheless, the data suggest that 35 of 388 patients (9%) developed acute myeloid leukemia, and one had acute lymphoblastic leukemia at diagnosis. Eighty-seven per cent died within 3 months of diagnosis of leukemia. These proportions are comparable to those obtained from the literature review.

MYELODYSPLASTIC SYNDROME

The definition of MDS in pediatrics is not as clear as it is in adults [86,87]. Literature cases were included if they were classified by the authors as "preleukemic" or myelodysplastic," and/or had a cytogenetic clonal abnormality. There were at least 32 such cases, 31 of whom had abnormal clones (Table II), and 77% of whom had increased chromosome breakage. Marrow morphology was heterogeneous, including myelodysplastia (MDS) [20,38,47,62,63,81,88,89], refractory anemia (RA) [88–90], and refractory anemia with excess blasts (RAEB) [26,29,38,39,91] among the MDS cases with clones, as well as RA in one patient with MDS without a clone [88]. Abnormal clones were also seen in patients whose marrows were normal [29], aplastic [34,38,92–94], cellular [27,95], or not described [71]. Two of 3 patients with Sweet's syndrome had clonal cytogenetics [88]. MDS was detected at a mean age of 17 years (range, 5–31 years).

Seven of 32 patients with MDS and/or clonal marrows went on to develop leukemia within 2 years, while 17 died up to 12 years later from other causes, and 8 were alive without leukemia up to 3 years later. The mean age at death for those who died with MDS alone or MDS followed by leukemia was 18 years (range, 2–36 years), slightly older than in those with leukemia without MDS. In the IFAR report [18], 34 patients had MDS, defined as having 5–30% blasts in the marrow, or 5–20% blasts in the blood (these would be RAEB and RAEBIT in the French-American-British (FAB) classification [86]). Eight had a marrow transplant, 10 developed leukemia, and 9 died from hematologic complications at 0.5–6 years after diagnosis of MDS.

The question of whether MDS and/or clonal marrow cytogenetics really imply preleukemia has been raised by us previously [4,96], and remains uncertain. On an absolute basis, development of leukemia in 7 of 32 literature patients, in 10 of 34 patients in the IFAR who already had increased blasts, and in 1 of 6 of our own patients with a clonal cytogenetic abnormality (B.P. Alter, unpublished) is higher than the 9% leukemia cases overall. However, the time for this evolution to occur was sometimes long, and the larger numbers who were either alive or died from other reasons suggest that an abnormal clone may not mean that leukemia is inevitable. Correct interpretation of clonal findings is critical, since marrow transplant using a mismatched or unrelated donor remains a very high-risk procedure. The most recent analysis from the International Bone Marrow Transplant Registry indicates a 2-year probability of survival of 66% for FA patients with aplastic anemia with matched sibling donors, and of 29% for mismatched or unrelated donors [97].

The frequency of clonal abnormalities is not known, since many FA patients only have bone-marrow examinations when hematologic changes are noted. Annual marrow studies might help to determine the natural history of marrow chromosomes in FA. Our own limited investigations to date have found abnormal clones in 6 of 15 consecutive patients with adequate numbers of cells (40%), higher than in the report by Schaison et al. [29] of 4 of 35 patients (11%), in the IFAR findings of 23 of 68 patients (34%) [18], and in the 2 of 14 patients who

TABLE III. Clonal Cytogenetic Abnormalities in Bone-Marrow Cells From FA Patients

Rearrangements	Interval	Number of cells		Clinical[a]
		Abnormal	Total	
Case 1				
der dup(1)(q12q31)	0	20	39	Normal
der(18)?t(1;18)(q12;p11)		3		
del(6)(p21p24)		2		
der(4)t(4;?)(p15.4;?)	1 year	23	25	Normal
del(1)(p21)	2 years	6	8	Normal
der(18)t(1;18)(q12;p11)	2.5 years	19	21	MDS
der(18)t(1;18)(q12;p11)del(12)(p12.1)		2		
Case 2				
del(3)(q22q24)	0	7	13	Mod AA
46,XY	3 months	0	12	Mod AA
del(3)(q22q24)	8 months	8	23	MDS
del(3)(q22q24)	1.7 years	2	44	MDS
+13		1		
46,XY	2.7 years	0	39	MDS
Case 3				
der(2)?t(1;2)(q21;q33)	0	8	9	AA
der(2)?t(1;2)(q21;q33)	1.5 years	19	35	MDS mild
der(1)dup(1)(q12 or q21q24)		6		
der(2)?t(1;2)(q21;q33)	2.5 years	6	20	MDS mild
der(1)dup(1)(q12 or q21q24)		5		
Case 4				
der(X)t(X;3)(p22.2;q13)+3	0			
der(X)t(X;3)(p22.2;q13)+3	1.5 years	67	69	MDS
der(X)t(X;3)(p22.2;q13)+3del(7)(p15)		1		
der(X)t(X;3)(p22.2;q13)	4 years	20	20	MDS
Case 5				
+X+8+21	0	50	50	Normal
Case 6				
dup(1)(q23q44)	0	2	40	MDS

[a]Mod AA, moderate aplastic anemia; AA, aplastic anemia; MDS, myelodysplasia.

were studied prior to entering the recent G-CSF trial [98]. The proportion may turn out to be even higher when serial studies are done.

One of the components confounding this analysis is the observation that clonal abnormalities may be transient. There are four reports in the literature in which abnormalities disappeared and/or reappeared [4,39]. Trisomy 21 was replaced by a clone with −3,−12,+M1,+M2 [26]; an isochromosome 7q appeared, disappeared, and reappeared [89]; a derivative Y appeared and disappeared while a trisomy 8 remained constant [99]; and a t(1;4) was transient prior to the appearance of MDS [39]. Three of our own 6 patients with abnormal clones demonstrated transience (cases 1, 2, and 4 in Table III, involving t(1;18), del(3), and t(1;2)); only in case 1 was this followed by development of acute myelogenous leukemia; a minor clone on the first marrow examination disappeared for 2 years and then emerged as the major clone. None of the IFAR patients had transient clones, but serial data were available on only 8 patients [18]. One explanation for clonal transience is that the marrow is populated by amplification from a small number of stem cells at any given time. In patients with chromosomal instability, one or more stem cells and progeny may be marked by clonal abnormalities. At a later time point, one or more different stem cells may be amplified, with no or different cytogenetic markers.

The literature cases were analyzed to determine whether there is any pattern to the clonal anomalies (Fig. 2). In those cases who were leukemic when studied, half of those with a clone had involvement of chromosome 7, one fourth had involvement of chromosome 1, and the only others that recurred were in chromosomes 2, 6, 7, 8, 5, and 21. In those with MDS who did not have leukemia, there was a slight excess of involvement of chromosome 1. One of the 4 with an abnormal chromosome 7 did develop leukemia. The others with MDS which evolved had one or more clones involving chromosomes 1, 3, 12, 17, and 21, and unknown or marker chromosomes. The IFAR cases also had a preponderance of chromosome 7 losses amongst the leukemics, but abnormal 7s were also seen in patients without leukemia.

LIVER DISORDERS

Patients with FA are known to be at risk for development of liver diseases, including tumors (Table IV). This occurred in 5% of cases in the literature, in whom liver

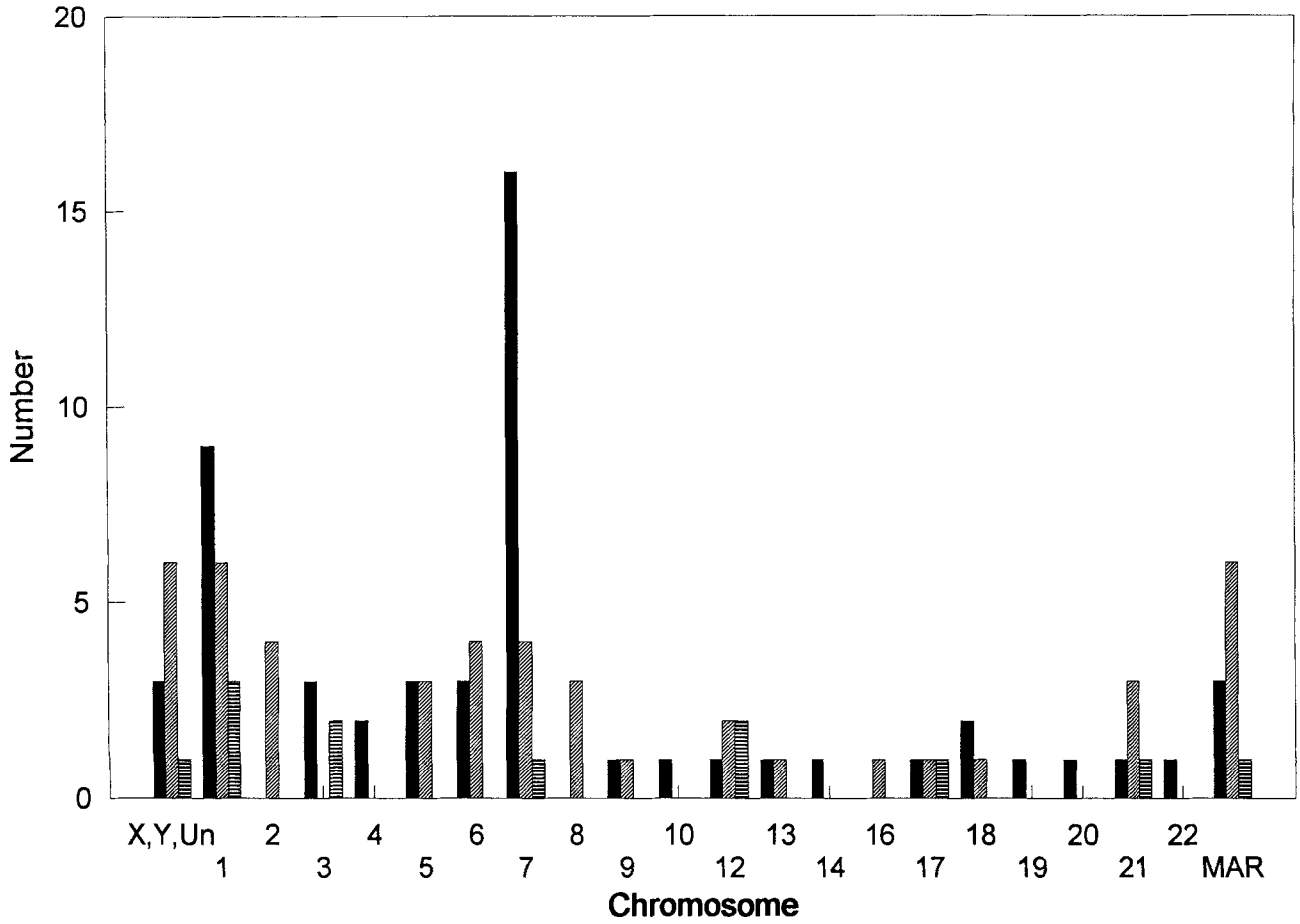

Fig. 2. Numbers of FA patients with each chromosome involved in cytogenetic clones. Solid columns, leukemia, 31 patients; hatched columns, MDS without leukemia, 25 patients; striped columns, MDS developing leukemia, 6 patients. Only the major clone was included if there were multiple clones.

disease was noted at a mean age of 16 years (range, 3–48 years). Only a single patient did not receive androgens [100], and thus the combination of androgens and a premalignant condition may predispose to liver complications. Fifty-seven per cent of patients with liver complications had increased chromosome breakage. Twenty patients had hepatocellular carcinomas [74,100–113], or hepatomas [47,114–118], of which 2 were called "benign" [25,119]. Two also had adenomas [74,113], and only one (the only one who also had increased alphafetoprotein) had metastases [100]. There were six adenomas [73,109,120–123], one of which was metastatic [120], and two tumors were not specified [32,123]. It is possible that the distinction between adenoma, hepatoma, and hepatocellular carcinoma is not entirely clear, just as the interpretation of a bone marrow as myelodysplastic is at times subjective. Associated tumors were tongue cancer [103], esophageal cancer [110], and leukemia [25,32, 47,73,74]. In at least 4 patients, liver tumors were found only at postmortem examination [107,112,117,121]. One patient had unexplained hepatic coma [42]. Seven had peliosis alone [104,124–128] (also, B.P. Alter, unpublished), and 6 had peliosis with a tumor [32,74, 106,110,112,114].

Discontinuation of androgens, including bone-marrow transplantation in some, led to improvement of liver findings [104,111,123,128]. More than 85% had died when reported, but from their underlying hematologic problems, and not directly from liver cancer. The mean age at death in these patients was 17 years, with a range of 3–48 years. The projected median was actually 13 years (Fig. 1).

CANCER

Other types of malignancies (solid tumors) which have been reported in FA are shown in Table V. These occurred in 45 patients (5%) who had a total of 55 tumors, at an average age of 23 years (range, 4 months–38 years). Sixty-seven per cent had documented increased chromosome breakage, while the rest were not investigated. There is an unexplained excess of females in this group, with a female:male ratio of 3:1 even after exclusion of the 11 patients with gynecologic tumors. Most had squamous-

TABLE IV. Liver Disorders in FA*

Type	Number	Male	Female
Adenoma (all)	7	4	3
Alone	3	2	1
With metastases	1	1	
"Benign"	3	1	2
Hepatocellular carcinoma (all), includes hepatoma	20	13	7
Hep ca	11	7	4
Hepatoma	4	3	1
Alone	15	10	5
Hep ca with adenoma	2	1	1
Hep ca with metastases	1		1
"Benign hepatoma"	2	2	
Tumor unspecified	2	1	1
Total tumors	29	18	11
Other (all)	2	1	1
Coma	1		1
Focal nodular hyperplasia	1	1	
Peliosis (all)	13	8	5
Alone	7	4	3
With tumor	6	4	2
Liver tumor and leukemia	5	4	1
Liver tumor and other cancer	2	1	1

*Hep ca, hepatocellular carcinoma.

TABLE V. Cancer in FA

Type	Number	Male	Female
Oropharyngeal	15	5	10
Cricoid	1		1
Gingiva	4	2	2
Gingiva, tongue	1	1	
Jaw, benign	1		1
Mandible	1		1
Pharynx	1	1	
Tongue	6	1	5
Gastrointestinal	16	4	12
Anus	4		4
Anus, Bowen's	1		1
Colon, anus	1		1
Esophagus	8	2	6
Gastric adenocarcinoma	2	2	
Gynecological	11		11
Breast	3		3
Cervix	1		1
Cervix, vulva	1		1
Vulva	6		6
Brain	4	1	3
Astrocytoma	2		2
Medulloblastoma	2	1	1
Other	9	1	8
Bone marrow lymphoma	1		1
Bronchopulmonary	1	1	
Eyelid, Bowen's	1		1
Renal	1		1
Skin	2		2
Bowen's	1		1
Wilms'	1		1
Retinoblastoma	1		1
Total	55	11	44

cell carcinomas. The most frequent tumors were oropharyngeal, including tongue [103,129–133], gingiva [134–136], gingiva and tongue [47], and one each of cricoid, benign jaw, mandible, and pharynx [131,137–139]. The next most common were gastrointestinal, involving the esophagus [110,134,140–146], anus [55,136,147–149], and colon [55], as well as stomach adenocarcinoma [150,151]. Gynecologic cancer occurred in one fourth of the patients, and involved the vulva [133,136,147, 152,153], breast [131,154,155], and cervix [131,156]; these occurred in women who had not had pregnancies as well as those who had [131]. Four patients had brain tumors [37,157], including two cousins [158], all at under age 5 years; only one of these was diagnosed antemortem, despite clinical signs of increased intracranial pressure. The eight other cancers occurred in seven different systems [38,42,92,131,149,157,159,160]. Two patients also had liver tumors [103,110], and one had leukemia [37].

At least 4 patients developed tongue cancer (one also had cheek cancer) following bone-marrow transplantation, after preparations which included irradiation [81,161–163]. There were 2 males and 2 females, and the tumors developed at 3–9 years after transplant. The limited data preclude an accurate prediction of the expected frequency of this complication, but it is at least 5% of the 50 or more long-term survivors of transplant.

It is difficult to manage cancer in patients with FA, since chemotherapy and/or radiation therapy leads to complications due to damage of other cells with a DNA repair defect. Surgery was the usual first approach, with the other modalities employed when surgery failed. More than 60% of patients were reported to have died, at an average age of 23 years, range 1–38 years. The projected median survival is age 28 years (Fig. 1).

IMPLICATIONS OF RISK OF MALIGNANCY

Table VI summarizes the characteristics of patients who developed malignant complications. The features of those with solid tumors need to be highlighted. These patients were older than the average FA patient when they developed their complications and were predominantly female. However, they were far younger than the average age at which these types of tumors are seen in individuals without FA. In most patients, FA was diagnosed many years prior to the appearance of cancer. The IFAR report [18] suggests that aplastic anemic occurs early in FA (actuarial risk of 84% after 20 years), followed by clonal cytogenetic abnormalities (risk of 67% by 30 years), and later by leukemia (risk for AML or MDS of 52% by age 40 years), with a risk of some hematologic problem of 98% by age 40 years. The risk of other cancers, namely

TABLE VI. Complications in Fanconi's Anemia*

	Leukemia	MDS	Other cancer	Liver disorders
Number of cases	84	32	45	37
Male:female ratio	1.3	1.1	0.3	1.6
Age at diagnosis of FA (years)				
Mean	10	13	12	9
Median	9	12	10	6
Range	0.1–28	1–31	0.1–32	1–48
Percentage ≥16	20	32	30	11
Age at complication (years)				
Mean	14	17	23	16
Median	14	17	26	13
Range	0.1–29	5–31	0.3–38	2.5–48
Interval from diagnosis to complication (years)				
Mean	4	7	11	7
Median	3	2	11	5
Range	0–19	0–31	0–29	0–24
Number without pancytopenia	21 (25%)	14 (44%)	8 (18%)	1 (3%)
Number without androgens	40 (48%)	20 (63%)	19 (42%)	1 (3%)
Number reported deceased	66 (79%)	24 (75%)	29 (64%)	32 (86%)

*One hundred forty-eight patients had one or more malignancy; the number of malignancies was 155. MDS cases include 7 who developed leukemia; the others are not included in the total. Four patients with tumors after bone marrow transplant are not included.

liver and solid tumors, was not presented in the IFAR report [18]. Our review of the literature (Table VI and Fig. 3) suggests that there is a progression with age, with a continuous change in risk for the patient who has not succumbed to earlier complications. The earliest risk is aplastic anemia, followed by leukemia, liver tumors, myelodysplasia and clonal abnormalities, and finally other cancers.

Recommendations are needed with regard to cancer surveillance in FA. Although it is not always clear what action should be taken when a problem is found (e.g., marrow clonal abnormalities), it is presumably better to be informed, and for leukemia or solid tumors early diagnosis must be better than late diagnosis. For hematologic changes, it is advised to undergo serial bone-marrow aspirations for morphology, biopsies for cellularity, and cytogenetic analyses for clonality. These might be done at least annually, as well as whenever unexplained changes are seen in the blood counts. The liver should be followed with liver enzyme tests every 2 months, and annual abdominal ultrasound examinations should be performed, particularly (but not exclusively) in patients receiving androgen treatment. If liver enzymes exceed 2–3 times normal, serious consideration should be given to discontinuation of androgens. Solid-tumor monitoring is more complex, since it encompasses a larger area of the body. Females who are past puberty perhaps should have twice-yearly breast and pelvic examinations, including Papanicolaou smears. All patients should have frequent oral scrutiny by their dentist and themselves. The lower pharynx, esophagus, and stomach can be evaluated with a mixture of upper endoscopy and barium swallows,

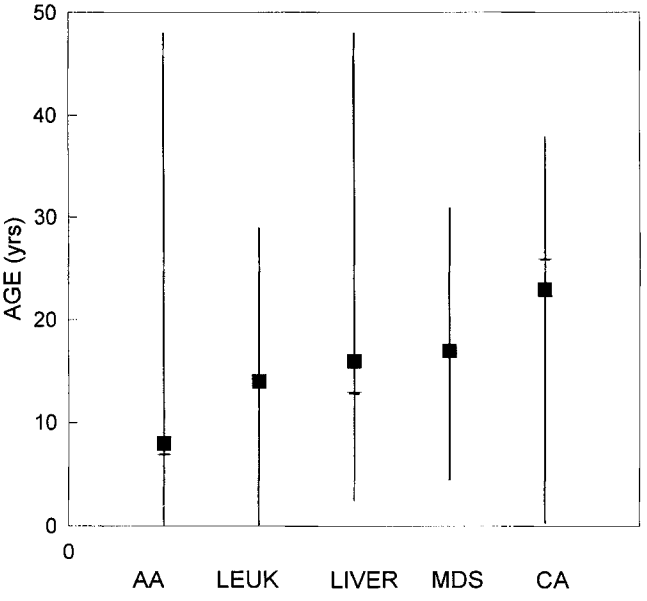

Fig. 3. Range of ages at which complications occurred in FA. ——, range; ■, mean; –, median.

depending on the tolerance of the patient to the former, and of the physician to the radiation exposure of the latter. The anal and rectal areas can be monitored with stool fecal blood tests as well as rectal examinations, and with sigmoidoscopy if indicated. Despite the rarity of skin cancer in FA, patients would be well-advised to avoid the sun and to use sunscreen. Brain tumors, which are rare and in young patients, need to receive a high index of suspicion in the patient with vomiting and/or headache.

The recommendations included here are merely suggestions, without data to demonstrate their effectiveness, but it is clear that patients with FA should be monitored more frequently than they currently appear to be. Careful surveillance will provide better incidence data, and offer the opportunity for earlier intervention (surgery, modified chemotherapy including the use of biologic response modifiers, and stem/progenitor transplant), as well as more accurate information regarding the natural history of FA and whether certain conditions warrant risky treatments (e.g., clonal marrows and unrelated transplants).

Bone-marrow transplant may cure aplastic anemia in FA patients, and may prevent or cure myelodysplasia or leukemia, but there may be an increased risk for cancer, perhaps related to the method of immunosuppression. Gene therapy, which is just beginning, may not even prevent MDS or leukemia, unless the treated stem cells gain a selective growth advantage over residual untreated cells [5]. If either procedure enables FA patients to live longer, they may now be at an even higher risk for solid tumors, which appear to be the disease of the older patient. When the transplanted or gene-treated FA patient tells me, "I don't have FA anymore," I have to say, "Probably not in your bone marrow." Nonhematopoietic systems remain at risk, and the incidence and types of malignancies may increase as our treatment of the hematopoietic defect improves. Is this a new Pandora's box?

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